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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/486,613	02/29/2000	DEBORAH C. MASH	N08-002	8931
7590	04/30/2004		EXAMINER	
COLEMAN SUDOL SAPONE P C				JIANG, SHAOJIA A
714 COLORADO AVENUE				
BRIDGEPORT, CT 06605-1601				
ART UNIT		PAPER NUMBER		
		1617		

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/486,613	MASH, DEBORAH C.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 12 September 2003 and 11 December 2003.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,2,4-9 and 25-30 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-2, 4-9, and 25-30 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                     | Paper No(s)/Mail Date. _____ .  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|  | 6) <input type="checkbox"/> Other: _____ .                                  |

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 11, 2003 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed December 11, 2003, and amendments and response filed September 12, 2003 and December 11, 2003, wherein claims 1-2 and 4-9 have been amended, and claim 3 is cancelled, and claims 25-30 are newly submitted.

Currently, claims 1-2, 4-9, and 25-30 are pending in this application.

It is noted that claims 10-24 are cancelled previously.

Claims 1-2, 4-9, and 25-30 are examined on the merits herein.

As indicated in the previous Office Action July 16, 2002, this application is a 371 of PCT/US98/18284 which claims priority to provisional application Serial No. 60/057,921.

***Claim Objection***

Claims 27-28 and 29-30 are objected under 37 CFR 1.75 as being a duplicate of claims. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

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***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-5, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment with respect to the amended claims 1-2 and 4-5, and new claims 25-30 has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for the negative limitation, "a patient to alleviate pain without addition". The original specification merely discloses treating a patient to alleviate pain broadly (see the specification and the claims as originally filed).

Any negative limitation or exclusionary proviso must have basis in the original disclosure. See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. See MPEP § 2163 - § 2163.07(b) for a discussion of the written description requirement of 35 U.S.C. 112, first paragraph.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epstein et al. (3,715,361, PTO-1449 submitted May 23, 2000) and GB 841,697 (PTO-1449 submitted May 23, 2000) in view of Bagal et al. (PTO-1449 submitted May 23, 2000) and Hussain (4,464,378, PTO-892) and Applicant's admission regarding the prior art in the specification (see page 1-3).

Epstein et al. discloses that ibogaine and its derivatives are analgesic agents (analgetics), and these agents are therefore useful in treating or alleviating pain. See abstract, col.1 lines 25-38, col.2 lines 1-10 and 33-35 and col.3 lines 1-4. The effective amounts or doses of ibogaine and its derivatives range from 25 mg –250 mg per kg of body weight (see tables at col.2 lines 58-65 and col.3).

GB 841,697 discloses that ibogaine is an analgesic agent, and is therefore useful in an analgesic composition for treating or alleviating pain. The effective amount or dose of ibogaine, 20-40 mg, is also taught in GB 841,697. See abstract, col.1-2, and claims 1-5.

The prior art does not expressly disclose the employment of noribogaine alone or in combination with an opioid antagonist such as naloxone, naltrexone and nalorphine in a method of treating a patient to alleviate pain. The prior art does also not expressly disclose the effective amounts of active agents in the composition herein to be administered.

Bagal et al. discloses that noribogaine is a known active metabolite of ibogaine, and noribogaine enhanced morphine antinociception was more pronounced than with comparable ibogaine treatment. See abstract and page 261 the last paragraph of the right column. The effective amount or dose of noribogaine is 40 mg per kg of body weight is also disclosed by Bagal et al. (see abstract for example).

Note that noribogaine is known to be 10-Hydroxyibogamine, a de-methyl-ibogaine; ibogaine is 10-methoxyibogamine. Thus, one of ordinary skill in the art would

clearly recognize that noribogaine is metabolite of ibogaine, which was necessarily produced in the patient's body upon ingestion of ibogaine by hydrolysis.

Hussain teaches that opioid antagonists such as naloxone, naltrexone and nalorphine are well known analgesics and therefore useful in a method of treating or alleviating pain in a patient. See col.1 lines 44 and 56-57, col.3 lines 24-27, and claims 1-2.

Applicant's admission regarding the prior art in the specification (see page 3) teaches that noribogaine is a known metabolite of ibogaine and opioid antagonists such as naloxone, naltrexone and nalorphine are known analgesics and useful in a method of treating or alleviating pain in a patient.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ noribogaine alone or in combination with an opioid antagonist such as naloxone, naltrexone and nalorphine in a method of treating a patient to alleviate pain, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ noribogaine alone or in combination with an opioid antagonist such as naloxone, naltrexone and nalorphine in a method of treating a patient to alleviate pain since noribogaine is a known active metabolite of ibogaine. Ibogaine is well known an analgesic agent and is known to be useful in treating or alleviating pain based on the prior art. Therefore, one of ordinary skill in the art would have reasonably expected that noribogaine, a known active metabolite of ibogaine,

would have the same therapeutic usefulness being an analgesic agent as ibogaine in the instant method for treating a patient to alleviate pain, since noribogaine was necessarily produced in the patient's body upon ingestion of ibogaine by hydrolysis. Moreover, noribogaine is known to possess more effective treatment in the morphine antinociception than ibogaine according to Bagal et al. Hence, Bagal et al. has also provided the motivation to employ noribigaine in the claimed method.

Further, opioid antagonists such as naloxone, naltrexone and nalorphine are well known to be useful in a method of treating a patient to alleviate pain. Therefore, one of ordinary skill in the art would have reasonably expected that combining noribogaine and an opioid antagonist herein known useful for the same purpose (i.e., treating a patient to alleviate pain) in a composition to be administered would improve the therapeutic effect for alleviating pain. Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active ingredients in the composition because the effective amounts of noribogaine and an opioid antagonist herein are known in the art. In addition, the optimization of amounts of active agents to be administered is considered well within the skill of artisan.

Since all active composition components herein are known to useful to treat a patient to alleviate pain, it is considered *prima facie* obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Thus the claimed invention as a whole is clearly *prima facie* obvious over the combined teachings of the prior art.

***Response to Argument***

Applicant's arguments filed December 11, 2003 with respect to the same rejection made under 35 U.S.C. 103(a) of record in the previous Office Action April 9, 2004 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art. These remarks are believed to be addressed by the obvious rejection presented above.

Additionally, Applicant argues that "The present invention relates to the unexpected discovery that noribogaine, in contrast to ibogaine". As discussed above, noribogaine is known to be 10-Hydroxyibogamine, a de-methyl-ibogaine; ibogaine is 10-methoxyibogamine. Thus, one of ordinary skill in the art would clearly acknowledge that noribogaine is metabolite of ibogaine, which was necessarily produced in the patient's body upon ingestion of ibogaine by hydrolysis in the body. Note that the court ruled that the metabolite of loratadine called descarboethoxyloratadine or "DCL" was INHERENTLY anticipated by loratadine (Claritin™) because it was necessarily produced in the patient's body upon ingestion of Claritin™. See Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003).

Therefore, one of ordinary skill in the art would have reasonably expected that noribogaine, a known active metabolite of ibogaine, would have at least the same therapeutic usefulness, and the same or substantially similar therapeutic effects being

an analgesic agent as ibogaine in the instant method for treating a patient to alleviate pain. Moreover, Bagal teaches that "This finding suggests the possibility that noribogaine alone induced an antinociceptive response that was additive with that of morphine" and "also suggestive of noribogaine-induced analgesia" (see page 260 at the middle of right column) (emphases added). Bagal et al. discloses that noribogaine enhanced morphine antinociception was more pronounced than with comparable ibogaine treatment. Hence, Bagal et al. has clearly provided the motivation to employ noribogaine alone and in the combination in the claimed method.

Applicant argues that ibogaine per se did not have analgesic effects, but Applicant also admits that Epstein discloses a series of acyl derivatives of 10-methoxyibogamine (known as ibogaine) analogs for use as potential analgesic/anti-inflammatory analogs. Evidence showing that ibogaine per se did not have analgesic effects is absent. Note that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

Moreover, one of ordinary skill in the art would appreciate that Epstein et al. discloses that a series of acyl derivatives of 10-methoxyibogamine (ibogaine) analogs are useful as analgesic agents as ibogaine.

Applicant's data in the Examples of the specification at pages 9-10 have been fully considered with respect to the obviousness of the claimed invention and but are not deemed persuasive. The results on the tests of the employment of the noribogaine

applied to a rat alone and in the combination have been taught and suggested by the cited prior art herein as discussed above. Therefore, the results herein are clearly expected and not unexpected based on the cited prior art. Expected beneficial results are evidence of obviousness. See MPEP § 716.02(c). Therefore, the evidence presented in Examples herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is 571.272.0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on 571.272.0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

  
S. Anna Jiang, Ph.D.  
Patent Examiner, AU 1617  
April 23, 2004